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(54) Cyclic amino acid derivatives

(71) Warner-Lambert Company

(72) Hartenstein, J., Satzinger, G., and Herrmann, M.F.R.

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(57) Claim 1. Compounds of general formula I in which R_1 represents hydrogen or methyl; R_2 represents C_1-C_8 straight or branched alkyl, C_1-C_8 cycloalkyl furfuryl, thiophene-methyl or benzyl either unsubstituted or substituted by one or more C_1-C_3 methyl, C_1-C_3 alkoxy, hydroxy, halogen or C_1-C_3 alkylene dioxy; R_3 represents hydrogen or C_1-C_8 straight or branched alkyl; n is 4, 5 or 6; and the pharmaceutically acceptable salts thereof.

Australia
Patents Act 1952-1973

508229

Convention Application for a Patent

We, WARNER-LAMBERT COMPANY, a corporation of the State of Delaware,

of 201 Tabor Road, Morris Plains, New Jersey, United States of America

hereby apply for the grant of a Patent

for an invention entitled "CYCLIC AMINO ACID DERIVATIVES"

which is described in the accompanying complete specification.

This application is a Convention application and is based on the application numbered P 26 26 467.5 for a patent or similar protection made in Federal Republic of Germany on 12th June, 1976.

10 JUN 1977 PATENT OFFICE

FEE STAMPS TO VALUE OF $80 ATTACHED. $ NAVAL OFFICER

Our address for service is: CALLINAN & ASSOCIATES Patent Attorneys, of 48-50 Bridge Road, Richmond, State of Victoria, Australia.

Dated this 9th day of June 19 77.

WARNER-LAMBERT COMPANY
By its Patent Attorneys:
CALLINAN AND ASSOCIATES

CALLINAN and ASSOCIATES
Patent and Trade Mark Attorneys
Post Office Box No. 234, Kent Town, South Australia

AUSTRALIA
No legalization required

Regulation 11 (1)
Regulation 11 (2)

AUSTRALIA
Patents Act 1952-1973

Declaration in Support of
(a) A Convention Application
(b) ~~An Application~~
for a Patent ~~or Patent of Addition~~

26024/77

In support of the ~~Application~~/Convention Application made by

(c) WARNER-LAMBERT COMPANY

for a patent ~~of addition~~ for an invention entitled:

(d) "CYCLIC AMINO ACID DERIVATIVES"

I/~~We~~ (e) ALBERT H. GRADDIS

of (f) 201 Tabor Road, Morris Plains, New Jersey 07950, United States of America

do solemnly and sincerely declare as follows:—

1. (g) ~~I am/we are the applicant(s) for the patent/patent of addition~~

or

(h) I am ~~we are~~ authorised by WARNER-LAMBERT COMPANY

the applicant for the patent/~~patent of addition~~ to make this declaration on its behalf.

2. (i) The basic application(s) as defined by Section 141 of the Act was/were made in The Federal Republic of Germany on the 12th day of June 1976

~~by~~ by GÖEDECKE AG.

3. (j) ~~I am/we are the actual inventor(s) of the invention~~

~~or~~

(k) ~~I am/we are the actual inventor(s) of the invention referred to in the basic application~~

~~or~~

Johannes HARTENSTEIN of Fohrenbühl, 23, 7801 Stegen-Wittental
Gerhard SATZINGER, of Im Mattenbühl, 7809 Denzlingen
and Manfred Franz Reinhold HERRMANN of Wolfweg 25, 7811 St. Peter, all of The Federal Republic of Germany.

(l)

~~or~~

H/are the actual inventor(s) of the invention and the facts upon which ~~I/we are~~/the said Company is entitled to make the application are as follows:

(m) The said company would, if a patent were granted upon an application made by the said actual inventors, be entitled to have the patent assigned to it, and is the assignee of priority right from the aforesaid basic applicant.

4. The basic application referred to in paragraph 2 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

(n) Declared at Morris Plains, this 9th day of May 1977

(a) Delete for Non-Convention Applications.
(b) Delete for Convention Applications.
(c) Insert Full Name of Applicant.
(d) Insert Title of Invention.
(e) Insert Full Name of Declarant(s).
(f) Insert Address(es) of Declarant(s).
(g) Delete where Applicant is a Company.
(h) Delete where Applicant is an Individual. Fill in Name of Applicant if a Company.
(i) For Non-Convention Applications delete. For Convention Applications, fill in details of basic application.
(j) Delete for Non-Convention Applications by Assignee of Inventor and for Convention Applications.
(k) Delete for Non-Convention Applications by Inventor and for Convention Applications by Assignee.
(l) Delete for Applications by Inventor(s). For Applications by Assignee, insert name, address and occupation of Inventor.
(m) Insert details of Assignment, Devolution of Application and/or Entitlement.
(n) Delete for Non-Convention Applications.

508229

ORIGINAL

This document contains the amendments made under Section 49.

and is correct for printing.

WARNER-LAMBERT COMPANY

AUSTRALIA

The Patents Act 1952-1973

COMPLETE SPECIFICATION FOR THE INVENTION ENTITLED:

"CYCLIC AMINO ACID DERIVATIVES"

The following statement is a full description of this invention, including the best method of performing it known to us:.

The present invention relates to N-substituted cyclic amino acid derivatives and to processes for the preparation thereof.

The N-substituted cylic amino acid derivatives according to the present invention are compounds of general formula I (of the accompanying drawings) in which: R_1 represents hydrogen or methyl; R_2 represents C_1-C_8 straight or branched alkyl, C_1-C_8 cycloalkyl, furfuryl, thiophene-methyl or benzyl either unsubstituted or substituted by one or more C_1-C_3 methyl, C_1-C_3 alkoxy, hydroxy, halogen or C_1-C_3 alkylene dioxy; R_3 represents hydrogen or C_1-C_8 straight or branched alkyl; n is 4, 5 or 6; and the pharmaceutically acceptable salts thereof.

~~The present invention relates to new N-substituted~~ cyclic amino acid derivatives and with processes for the preparation thereof.

The N-substituted cyclic amino acid derivatives according to the present invention are compounds of the general formula I (as shown in the accompanying drawings) wherein R_1 is a hydrogen atom or a methyl radical, R_2 is a lower alkyl or cycloalkyl radical, or a benzyl radical, the aromatic nucleus of which may be substituted, or a furfuryl- or thiophene-methyl radical, R_3 is a hydrogen atom or a lower alkyl radical and n is 4, 5, or 6; and the pharmacologically ~~compatible salts thereof.~~

By lower alkyl radicals, there are to be understood straight-chained or branched alkyl radicals containing up to 8 carbon atoms. Preferred lower alkyl radicals contain up to 5 carbon atoms, especially the methyl, ethyl, isopropyl, n-butyl and isopentyl radicals.

Those compounds of formula (I) are preferred in which R_1 is a hydrogen atom or a methyl radical, R_2 is an alkyl radical containing up to 5 carbon atoms or a benzyl radical and R_3 is a hydrogen atom or a methyl or ethyl radical.

The compounds encompassed by the general formula (I) exhibit hypothermal and, in some cases, narcosis-potentiating or sedating properties. They are also characterized by an extremely low toxicity. In animal experiments, there was, surprisingly, also found a remarkable protective effect against cramp induced by thiosemicarbazide. Some of the

compounds also possess a considerable protective action against cardiazole cramp. These new compounds (I) can be used for the therapy of certain cerebral diseases, for example, they are suitable for the treatment of certain forms of epilepsy, dizziness, of hypokinesia and cranial trauma. They also bring about an improvement of the cerebral functions. Consequently, they are also especially effective in the treatment of geriatric patients.

The present invention also provides a process for the preparation of compounds of general formula which comprises reductive N-alkylation of compounds of the general formula II wherein R_4 is a hydrogen atom or a lower alkyl radical and n is 4, 5, or 6, followed, if desired, by esterification or transesterification with an alcohol of the general formula III wherein R_2 is a hydrogen atom or a lower alkyl. If desired, the compounds thus obtained may be further converted into their pharmacologically compatible salts by reaction with appropriate acids or bases.

The N-alkylation according to the present invention is carried out by known processes (see Houben-Weyl, Vol. 11/2, p. 330) by first reacting the compounds of general formula (II) with a carbonyl compound which contains a number of carbon atoms corresponding to the radical R_1 or R_2. After the intermediate compound is obtained, it is then converted into the desired end product by means of a reducing agent.

The reaction can be carried out in an inert solvent and, as reducing agent, there can be used, for example, formic acid, catalytically activated hydrogen, or a metal hydride,

such as sodium borohydride or sodium cyanoborohydride.

Examples of carbonyl compounds which can be used include the aliphatic aldehydes, such as formaldehyde, acetaldehyde, propionaldehyde, isobutyraldehyde, butyraldehyde and valeraldehyde, and the ketones, such as acetone, methyl ethyl ketone, methylpropyl ketone, diethyl ketone, cyclohexanone, cyclopentanone and cycloheptanone.

Examples of aromatic aldehydes, which can be used encompass benzaldehyde, halogenated aldehydes, such as chlorobenzaldehyde or bromobenzaldehyde, tolualdehyde, mono- and dihydroxybenzaldehyde, methoxybenzaldehyde, di- and trimethoxybenzaldehydes, such as veratraldehyde, piperonal and 3,4,5- trimethoxybenzaldehyde, and hydroxymethoxybenzaldehydes, such as vanillin or isovanillin, as well as furfural or thiophene-aldehyde.

When using the carbonyl compound formaldehyde, the corresponding N-methyl or N,N-dimethyl compounds are obtained, whereas the other aldehydes yield only the N-monosubstituted compounds. The N,N-mixed substituted compounds are, therefore, prepared by first carrying out a reductive alkylation with a carbonyl compound which possesses a number of carbon atoms corresponding to the radical R_2 and then introducing the methyl radical R_1 by means of formaldehyde.

Compounds of general formula (I) in which R_1 is a hydrogen atom and R_2 is a methyl radical can be prepared by reductively N-methylating the N-benzyl compound by means

of formaldehyde and subsequently splitting off the benzyl radical hydrogenolytically in the presence of a catalyst such as palladium charcoal or platinum oxide.

For the preparation of the compounds of general formula (I), the compounds of formula (II) are reacted with equivalent or excess amounts of a carbonyl compound in an inert solvent. The carbonyl compound may also serve as the solvent. The intermediate is then hydrogenated in the presence of a catalyst, such as palladium-charcoal or platinum oxide, at ambient or a moderately elevated temperature, preferably at 20 to 50°C. The hydrogenation can be carried out at a hydrogen pressure of about 1 to 5 atmospheres. The reductive alkylation, especially the methylation or benzylation, may be carried out in such a manner that the intermediate formed by the reaction with a compound of general formula (II) is reduced with sodium borohydride (see Helv. Chim. Acta., 46, 327/1963) or sodium cyanoborohydride (see J. Org. Chem., 37, 1673/1972); the reaction is preferably carried out at a temperature of from 0 to 25°C. and in a polar solvent such as water, methanol, ethanol, dioxan, tetrahydrofuran, acetonitrile or aqueous mixtures of these solvents.

N-methylation can also be accomplished by reductive alkylation of the monosubstituted amine with a carbonyl compound, such as formaldehyde, and formic acid or formamides as reducing agents. (See Houben-Weyl, vol. 11/2, p. 331).

When R_3 is to be an alkyl radical the carboxyl group of the amino acid obtained is esterified. The reaction is, most simply, carried out by dissolving the free amino acid of formula (I) or a salt thereof in an excess of the esterifying alcohol and saturating the solution with hydrogen chloride. The amino acid ester hydrochloride is thus directly obtained.

The compounds of general formula (II) used as starting materials can be prepared by one of the following methods:

(a) converting a compound of the general formula IV wherein R_5 is an alkyl radical containing up to 8 carbon atoms and n is 4, 5, or 6, via a reactive acid derivative, into an azide and then subjecting this to the Curtius rearrangement; or

(b) subjecting a compound of the general formula V in which n is 4, 5, or 6 to the Hofmann rearrangement; or

(c) subjecting a compound of the general formula VI wherein n is 4, 5, or 6, or a compound of the general formula VIa wherein n is 4, 5, or 6, to the Lossen rearrangement.

When a free amino acid is obtained, it may be esterified to give a corresponding lower alkyl ester and/or the product obtained may be converted into a pharmaceutically compatible salt by reaction with an acid or a base.

The reaction of the compounds of general formula (IV) takes place according to the well-known Curtius rearrangement.

The free carboxyl group is first activated by conversion into a reactive derivative, for example an acid halide or a mixed anhydride, and subsequently reacted with an appropriate azide, for example, sodium azide. The acid azide thus obtained is then subjected to thermal decomposition in an organic solvent, for example, benzene, toluene or an alcohol, such as ethanol, during which nitrogen is split off and an intramolecular rearrangement to an isocyanate or, in the presence of an alcohol, to a urethane takes place. The isocyanates and the urethanes can easily be converted into the desired primary amines by basic or acidic hydrolysis.

The well-known Hofmann rearrangement of compounds of general formula (V) also takes place via isocyanates. In this case, the acid amides are reacted with alkali metal hypohalites. Upon hydrolysis of the isocyanate formed by anionotropic rearrangement, the desired amine is formed, together with carbon dioxide.

The Lossen rearrangement of the hydroxamic acids of general formula (VI) also takes a similar course. In this case, water is split off, the corresponding isocyanate first being formed, hydrolysis of which gives the desired amine.

Usually the hydroxamic acids are reacted with bases via their O-acyl derivatives as, for example, the O-acetyl-, O-benzoyl- and preferably O-sulfonyl- derivatives.

The compounds of general formula (VIa) can be prepared by reacting a hemiester of the general formula VIb wherein

R_3 is an alkyl radical containing up to 5 carbon atoms and n is 4, 5, or 6, with hydroxylamine at an elevated temperature, preferably of from 50 to 100°C. (See J.C.S., 1929, 713).

Since amino acids are amphoteric, pharmacologically compatible salts when R_3 is a hydrogen atom, can be salts of appropriate inorganic or organic acids, for example, hydrochloric acid, sulphuric acid, phosphoric acid, acetic acid, oxalic acid, lactic acid, citric acid, malic acid, salicylic acid, malonic acid, maleic acid, succinic acid or ascorbic acid, but also, starting from the corresponding hydroxides or carbonates, salts with alkali metals or alkaline earth metals, for example, sodium, potassium, magnesium or calcium. Salts with quaternary ammonium ions can also be prepared with, for example, the tetramethyl-ammonium ion. Of course, when R_3 is a lower alkyl radical, it is only possible to form salts with acids.

The compounds of general formula (IV) used as starting materials can be prepared by reacting an acid anhydride of the general formula VII wherein n is 4, 5, or 6, either with water, or with one mole of an alcohol of the general formula VIII wherein R_5 has the same meaning as above.

The compounds of general formula (VII) are known (See J.C.S., 115, 686/1919; Soc., 99, 446; J.C.S., 117, 639/1920).

Some of the compounds of general formula (V), as well as processes for the preparation thereof, are known (see

Austral. J.C., 13, 127/1960). They can also be prepared, for example, by reacting compounds of general formula (VII) with ammonia. In this case it is advantageous to operate at the lowest possible temperature. However, it is also possible, as described above, to prepare a hemiester and to react the free carboxyl group with, for example, ethyl chloroformate and subsequently with ammonia.

The hydroxamic acids of general formula (VI) can be obtained analogously by reaction of the anhydride (VII) with hydroxylamine.

Because of their low toxicity, the compounds of general formula (I) according to the present invention can be administered enterally or parenterally within wide dosage limits in solid or liquid form. As injection solution, water which contains the additives usual in the case of injection solutions, such as stabilizing agents, solubilizing agents or buffers is preferably employed.

Additives of this type include, for example, tartrate and citrate buffers, ethanol, complex-forming agents such as ethylenediamine-tetraacetic acid and the non-toxic salts thereof, as well as high molecular weight polymers such as liquid polyethylene oxide for viscosity regulation. Solid carrier materials include, for example, starch, lactose, mannitol, methyl cellulose, talc, highly dispersed silicic acids, high molecular weight fatty acids such as stearic acid, gelatine, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable fats and solid high molecular weight

polymers such as polyethylene glycol. Compositions which are suitable for oral administration can, if desired, also contain flavoring and/or sweetening agents.

The individual dosage for the compounds according to the present invention are preferably 5 - 50 mg. parenterally and 20 - 200 mg. enterally.

Thus, the present invention also provides pharmaceutical compositions containing at least one compound of general formula (I) and/or at least one pharmaceutically compatible salt thereof in admixture with a solid or liquid pharmaceutical diluent or carrier.

The following Examples are given for the purpose of illustrating the present invention:

EXAMPLE 1

1-(N,N-Dimethylaminomethyl)-cyclohexane-acetic acid.

4.5 g. 1-aminomethylcyclohexane-acetic acid are dissolved in 150 ml. water and mixed with 8.5 ml. 37% aqueous formaldehyde solution. The reaction mixture is hydrogenated in the presence of palladium-charcoal (10%) at ambient temperature and atmospheric pressure. The calculated amount of hydrogen is taken up after 3 hours. The reaction mixture is filtered and the filtrate acidified to pH 2 with dilute hydrochloric acid and then concentrated in a vacuum. By crystallisation of the residue from acetone/diethyl ether, there are obtained 4.9 g. (79% of theory) 1-(N,N-dimethylaminomethyl)-cyclohexane-acetic acid in the form of its hydrochloride; m.p. 140 - 142°C.

Analysis:

$C_{11}H_{21}NO_2.HCl.1/4H_2O$

calc. :	C 54.99%;	H 9.44%;	N 5.83%;	Cl 14.76%
found:	54.90%;	9.36%;	6.22%;	15.05%

The 1-aminomethylcyclohexane-acetic acid used as starting material is prepared as follows:

5.6 ml. triethylamine in 16 ml. anhydrous acetone is added dropwise, with stirring and cooling to 0°C., to a solution of 7.28 g. 1,1-cyclohexane-diacetic acid monomethyl ester in 60 ml. anhydrous acetone, followed by a solution of 3.6 ml. ethyl chloroformate in 16 ml. anhydrous acetone. Stirring is continued for 30 minutes at 0°C. and then a solution of 3.4 g. sodium azide in 12 ml. water is added thereto dropwise. The reaction mixture is further stirred for 1 hour at 0°C., then poured into ice-water and extracted three times with 50 ml. amounts of ice-cold toluene. The combined extracts are dried at 0°C. over anhydrous sodium sulphate and subsequently dropped into a flask pre-heated to 100°C. The mixture is further heated under reflux for 1 hour and then evaporated in a vacuum. The crude methyl 1-isocyanatomethyl-1-cyclohexane-acetate remaining behind is heated under reflux for 3 hours in 50 ml. 20% hydrochloric acid. After cooling the solution, the 1-aminomethyl-1-cyclohexane-acetic acid lactam formed as a by-product is removed by extracting three times with 100 ml. amounts of chloroform, whereafter the aqueous hydrochloric acid solution is evaporated in a vacuum. The

1-aminomethyl-1-cyclohexane-acetic acid crystallises out as the hydrochloride; m.p. 123 - 132°C., after recrystallisation from acetone/methanol/diethyl ether.

EXAMPLE 2

1-(N,N-Dimethylaminomethyl)-cycloheptane-acetic acid.

In a manner analogous to that described in Example 1, by the catalytic hydrogenation of a solution of 5.5 g. 1-aminomethyl-cycloheptane-acetic acid and 9.6 ml. 37% aqueous formaldehyde solution in 180 ml. water in the presence of 5.5 g. palladium-charcoal (10%) and corresponding working up, there are obtained 4.97 g. (67% of theory) 1-(N,N-dimethylaminomethyl)-cycloheptane-acetic acid in the form of its hydrochloride; m.p. 185 - 188°C.

Analysis:

$C_{12}H_{23}NO_2 \cdot HCl$

calc. :	C 57.70%;	H 9.68%;	N 5.61%;	Cl 14.19%
found :	57.75%;	9.60%;	5.51%;	14.23%

The 1-aminomethyl-cycloheptane-acetic acid used as starting material is prepared as follows:

13.7 g. 1,1-cycloheptane-diacetic anhydride are mixed with 2.36 g. anhydrous methanol in 10 ml. benzene and the mixture boiled under reflux for 2 hours. After evaporating the reaction mixture in a vacuum, there are obtained 15.9 g. 1,1-cycloheptane-diacetic acid monomethyl ester. This is dissolved in 100 ml. anhydrous acetone and, in a manner analogous to that described in Example 1, first mixed with 8.1 g. triethylamine in 30 ml. acetone

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and thereafter with 9.8 g. ethyl chloroformate in 30 ml anhydrous acetone and finally with 6.5 g. sodium azide in 20 ml. water. After the reaction has taken place, the reaction mixture is extracted in the manner described in Example 1 and the sclution obtained of 1,1-cycloheptane-diacetic acid monomethyl ester azide in toluene is re-arranged to give the corresponding isocyanate. The 1-isocyanatomethyl-1-cycloheptane-acetic acid methyl ester obtained is then boiled under reflux for 3 hours with 20% hydrochloric acid. Upon concentrating the reaction mixture in a vacuum, 1-aminomethyl-1-cycloheptane-acetic acid separates out in the form of its hydrochloride, which is recrystallised from methanol/acetone/ethyl acetate; m.p. 69 - 72°C.

EXAMPLE 3

1-(N-Isopropylaminomethyl)-cyclohexane-acetic acid.

5 g. 1-aminomethylcyclohexaneacetic acid hydrochloride are hydrogenated at ambient temperature in a mixture of 60 ml. water and 30 ml. acetone in the presence of 0.5 g. platinum oxide. The calculated amount of hydrogen is taken up after 5 hours. The catalyst is filtered off and the filtrate is evaporated in a vacuum. Crystallisation of the residue for isopropanol/acetone gives 5.2 g (88% of theory) 1-N-isopropylaminomethyl)-cyclohexaneacetic acid in the form of its hydrochloride; m.p. 175 - 180°C.

Analysis:

$C_{12}H_{23}NO_2.HCl$

calc. : C 57.70%; H 9.68%; N 5.61%; Cl 14.19%

found : 57.76%; 9.74%; 5.94%; 14.12%.

EXAMPLE 4

1-(N-Isopropylaminomethyl)-cycloheptane-acetic acid.

In a manner analogous to that described in Example 3, 1.11 g. 1-aminomethylcycloheptane-acetic acid hydrochloride is hydrogenated in a solution of 10 ml. water and 10 ml. acetone in the presence of 0.1 g. platinum oxide. After appropriate working up and crystallisation from isopropanol/acetone, there is obtained 1-(N-isopropylaminomethyl)-cycloheptane-acetic acid in the form of its hydrochloride: m.p. 193 - 194°C. (sublimes > 190°C.).

EXAMPLE 5

1-(N-n-Propylaminomethyl)-cyclohexane-acetic acid.

A solution of 0.86 g. 1-aminomethylcyclohexane-acetic acid in 1.16 g. propionaldehyde in 100 ml. 9% ethanol is hydrogenated at ambient temperature in the presence of 0.85 g. palladium-charcoal (10%). After 1 hour, the calculated amount of hydrogen is taken up. The catalyst is filtered off, the filtrate is acidified with dilute hydrochloric acid and then evaporated in a vacuum. Crystallisation from acetone/diethyl ether gives 1-(N-n-propylaminomethyl)-cyclohexane-acetic acid in the form of its hydrochloride; m.p. 146 - 152°C.

EXAMPLE 6

1-(N-n-Propylaminomethyl)-cycloheptane-acetic acid.

In a manner analogous to that described in Example 5, by the catalytic hydrogenation of 1.1 g. 1-aminomethyl-

cycloheptane-acetic acid and 1.16 g. propionaldehyde in 100 ml. ethanol in the presence of 1.16 g. palladium-charcoal (10%) at ambient temperature and appropriate working up, there is obtained 1-(N-n-propylaminomethyl)-cycloheptane-acetic acid; m.p. 182 - 183°C.

EXAMPLE 7

1-(N-Ethylaminomethyl)-cyclohexane-acetic acid.

In a manner analogous to that described in Example 5, by the catalytic hydrogenation of a solution of 0.86 g. 1-aminomethylcyclohexane-acetic acid and 2.2 g. acetaldehyde in 100 ml. methanol in the presence of 0.85 g. palladium-charcoal and appropriate working up, there is obtained 1-(N-ethylaminomethyl)-cyclohexane-acetic acid; m.p. 172 - 173°C., after recrystallisation from isopropanol/diethyl ether.

EXAMPLE 8

1-(N-Ethylaminomethyl)-cycloheptane-acetic acid.

In a manner analogous to that described in Example 5, by the catalytic hydrogenation of 1.85 g. 1-aminomethyl-cycloheptane-acetic acid and 2.2 g. acetaldehyde in 100 ml. ethanol in the presence of 1.85 g. palladium-charcoal and appropriate working up, there is obtained 1-(N-ethylaminomethyl)-cycloheptane-acetic acid in the form of its hydrochloride; m.p. 168 - 170°C.

EXAMPLE 9

1-(N-n-Butylaminomethyl)-cyclohexane-acetic acid.

In a manner analogous to that described in Example 5, by the catalytic hydrogenation of a mixture of 0.86 g.

1-aminomethylcyclohexane-acetic acid and 1.44 g. n-butyraldehyde in 50 ml. 95% ethanol in the presence of 0.8 g. palladium-charcoal, there is obtained 1-(N-n-butylaminomethyl)-cyclohexane-acetic acid; m.p. 142 - 154°C.

EXAMPLE 10

1-(N-n-Butylaminomethyl)-cycloheptane-acetic acid.

In a manner analogous to that described in Example 5, 0.93 g. 1-aminomethylcycloheptane-acetic acid are hydrogenated with 1.44 g. n-butyraldehyde in 50 ml. ethanol in the presence of 0.9 g. palladium-charcoal. After appropriate working up and crystallisation from acetone/diethyl ether, there is obtained 1-(N-n-butylaminomethyl)-cycloheptane-acetic acid in the form of its hydrochloride; m.p. 158 - 165°C.

EXAMPLE 11

1-(N-Benzylaminomethyl)-cyclohexane-acetic acid.

Variant A.

0.86 g. 1-aminomethylcyclohexane-acetic acid are hydrogenated in 50 ml. 95% ethanol with 0.65 g. benzaldehyde in the presence of 0.1 g. platinum oxide. The reaction mixture is worked up in the manner described in Example 5. After crystallisation from acetone/diethyl ether, there is obtained 1-(N-benzylaminomethyl)-cyclohexane-acetic acid in the form of its hydrochloride; m.p. 125 - 135°C.

Variant B.

386 g. sodium 1-aminomethylcyclohexane-acetone in 2 ml. water, prepared from the free amino acid by the

addition of an equivalent amount of sodium hydroxide in water, are mixed with 0.21 ml. benzaldehyde. The reaction mixture is stirred at ambient temperature until the solution is homogeneous. Subsequently, 75 mg. sodium cyanoborohydride are introduced portionwise, while stirring. After stirring for one hour, the reaction mixture is acidified with dilute hydrochloric acid and evaporated in a vacuum. After crystallisation of the residue from acetone/diethyl ether, there is obtained 1-(N-benzylaminomethyl)-cyclohexane-acetic acid, the hydrochloride of which melts at 125 - 135°C.

EXAMPLE 12

1-(N-Benzyl-N-Methylaminomethyl)-cyclohexane-acetic acid.

500 mg. 1-(N-Benzylaminomethyl)-cyclohexane-acetic acid hydrochloride (cf. Example 11) are dissolved in 10 ml. water and mixed with 1.68 ml. 1N aqueous sodium hydroxide solution. This solution is introduced into a prehydrogenated solution of 500 mg. platinum dioxide in 10 ml. water. After the addition of 1 ml. 37% aqueous formaldehyde solution, hydrogenation is carried out at ambient temperature and atmospheric pressure. After about 2 hours, the take up of hydrogen ceases. The catalyst is filtered off and the filtrate, after acidification with dilute hydrochloric acid, is evaporated in a vacuum. Excess formaldehyde is removed by repeated evaporation with water. Crystallisation of the residue from acetone/diethyl ether gives 1-(N-benzyl-N-methylaminomethyl)-cyclohexane-acetic acid hydrochloride; m.p. 150 - 157°C.

EXAMPLE 13

1-(N-Methylaminomethyl)-cyclohexane-acetic acid.

178 mg. 1-(N-benzyl-N-methylaminomethyl)-cyclohexane-acetic acid hydrochloride are hydrogenated in 25 ml. ethanol in the presence of 0.2 g. palladium-charcoal at ambient temperature and atmospheric pressure. After 1 hour, the catalyst is filtered off and the filtrate evaporated in a vacuum at 20°C. Crystallisation of the residue from acetone/diethyl ether gives 1-(N-methylaminomethyl)-cyclohexane-acetic acid in the form of its hydrochloride; m.p. 160 - 162°C.

EXAMPLE 14

1-(N-Ethyl-N-methylaminomethyl)-cycloheptane-acetic acid.

1 g. 1-(N-ethylaminomethyl)-cycloheptane-acetic acid hydrochloride (cf. Example 8) is dissolved in 60 ml. water and mixed with 4 ml. 1N aqueous sodium hydroxide solution. After the addition of 2 ml. 37% aqueous formaldehyde solution, the reaction mixture is hydrogenated in the presence of 1 g. palladium-charcoal at ambient temperature and atmospheric pressure. Afterabout 2 hours, the calculated amount of hydrogen is taken up. The reaction mixture is then worked up in the manner described in Example 12 and, after recrystallisation from acetone/diethyl ether, there is obtained 1-(N-ethyl-N-methylaminomethyl)-cycloheptane-acetic acid in the form of its hydrochloride; m.p. 148 - 153°C.

EXAMPLE 15

1-(N-Cyclohexylaminomethyl)-cycloheptane-acetic acid.

A solution of 925 mg. 1-aminomethylcycloheptane-acetic acid and 982 mg. cyclohexanone in 50 ml. 90% aqueous methanol is hydrogenated in the presence of 0.8 g. palladium-charcoal at ambient temperature and atmospheric pressure. After working up the reaction mixture in the manner described in Example 5 and crystallising from aqueous methanol, there is obtained 1-(N-cyclohexylaminomethyl)-cycloheptane-acetic acid hydrochloride; m.p. 198 - 204°C.

EXAMPLE 16

Ethyl 1-(N-ethylaminomethyl)-cycloheptane-acetate.

166 mg. 1-(N-ethylaminomethyl)-cycloheptane-acetic acid hydrochloride (cf. Example 8) are dissolved in 5 ml. absolute ethanol. Gaseous hydrogen chloride is passed in and the solution is left to stand overnight at ambient temperature. After evaporation in a vacuum and crystallisation of the residue from ethyl acetate/diethyl ether/hexane, there is obtained ethyl 1-(N-ethylaminomethyl)-cycloheptane-acetate in the form of its hydrochloride; m.p. 110 - 118°C.

EXAMPLE 17

A solution of 3 g. 1-aminomethylcycloheptane-acetic acid hydrochloride and 13.86 ml. 1N aqueous sodium hydroxide solution in 150 ml. ethanol is mixed with 3 g. freshly distilled benzaldehyde and hydrogenated in the presence of 2.3 g. platinum dioxide at ambient temperature

and atmospheric pressure. After working up the reaction mixture as described in Example 5 and crystallisation from aqueous ethanol, there is obtained 1-(N-benzylaminomethyl)-cycloheptane-acetic acid hydrochloride; m.p. 145 - 157°C.

The claims defining the invention are as follows:

1. Compounds of general formula I in which R_1 represents hydrogen or methyl; R_2 represents C_1-C_8 straight or branched alkyl, C_1-C_8 cycloalkyl, furfuryl, thiophene-methyl or benzyl either unsubstituted or substituted by one or more C_1-C_3 methyl, C_1-C_3 alkoxy, hydroxy, halogen or C_1-C_3 alkylene dioxy; R_3 represents hydrogen or C_1-C_8 straight or branched alkyl; n is 4, 5 or 6; and the pharmaceutically acceptable salts thereof.

~~The claims defining the invention are as follows:~~

~~1. Compounds of the general formula I wherein~~ R_1 is hydrogen or methyl, R_2 is lower alkyl or cycloalkyl of 1 to 8 carbons, benzyl, the aromatic nucleus of which can be substituted, furfuryl- or thiophene-methyl R_3 is hydrogen atom or lower alkyl of 1 to 8 carbons, n is 4, ~~5, or 6, and the pharmacologically compatible salts thereof.~~

2. Compounds according to Claim 1, wherein R_1 is hydrogen or methyl, R_2 is an alkyl containing up to 5 carbon atoms or benzyl, R_3 is hydrogen, methyl or ethyl, and n is 4, 5, or 6.

3. A compound selected from 1-(N,N-Dimethylaminomethyl)-cyclohexane-acetic acid;

1-(N,N-dimethylaminomethyl)-cycloheptane-acetic acid;

1-(N-Isopropylaminomethyl)-cyclohexane-acetic acid;

1-(N-Isopropylaminomethyl)-cycloheptane-acetic acid;

1-(N-n-Propylaminomethyl)-cyclohexane-acetic acid;

1-(N-n-Propylaminomethyl)-cycloheptane-acetic acid;

1-(N-Ethylaminomethyl)-cyclohexane-acetic acid;

1-(N-Ethylaminomethyl)-cycloheptane-acetic acid;

1-(N-n-Butylaminomethyl)-cyclohexane-acetic acid;

1-(N-n-Butylaminomethyl)-cycloheptane-acetic acid;

1-(N-Benzylaminomethyl)-cyclohexane-acetic acid;

1-(N-Benzyl-N-methylaminomethyl)-cyclohexane-acetic acid;

1-(N-Methylaminomethyl)-cyclohexane-acetic acid;

1-(N-Ethyl-N-methylaminomethyl)-cycloheptane-acetic acid;

1-(N-Cyclohexylaminomethyl)-cycloheptane-acetic acid;

Ethyl 1-(N-ethylaminomethyl)-cycloheptane-acetate; or

1-(N-Benzylaminomethyl)-cycloheptane-acetic acid.

4. A process for the preparation of compounds of the general formula I, as defined in claim 1, wherein a compound of the general formula II in which R_4 is a hydrogen atom or a lower alkyl radical and n is as defined in claim 1, is reductively N-alkylated and, if desired, subsequently esterified or transesterified with an alcohol of the general formula $HO.R_3$, in which R_3 is as defined in Claim 1.

5. A process for the preparation of compounds of formula I, in which R_1 is a hydrogen atom and R_2 is a methyl radical, wherein an ~~appropriate~~ (substituted or unsubstituted) N-benzyl compound of formula II is reductively N-methylated with formaldehyde and the benzyl radical then split off hydrogenolytically in the presence of palladium-charcoal.

6. A process according to claim 4 or 5, wherein the reductive N-alkylation is carried out with a carbonyl compound in equivalent or excess amount in an inert solvent in the presence of a hydrogenation catalyst.

7. A process according to any one of claims 4 to 6, wherein the reductive hydrogenation is carried out at a temperature of from 20 to 50°C.

8. A process according to claim 6 or 7, wherein the reductive hydrogenation is carried out at a pressure of from 1 to 5 ats.

9. A process according to any one of claims 4 to 8, wherein the product obtained is reacted with a pharmacologically-compatible inorganic or organic acid to give the corresponding salt.

10. A process according to any one of claims 4 to 8, wherein, when R_2 in the product obtained is a hydrogen atom, this is reacted with a pharmacologically-compatible base to give the corresponding salt.

11. Pharmaceutical compositions, comprising at least one compound of formula I, in admixture with a solid or liquid pharmaceutical diluent or carrier.

~~12. Method of treatment of epilepsy, dizziness, hypokinesia, cranial traumas and geriatric diseases which comprises administering an effective amount of at least one compound of formula I to a mammal.~~

12. An N-substituted cyclic amino acid derivative substantially as hereinbefore described with reference to any one of the Examples.

13. A process for preparing an N-substituted cyclic amino acid derivative substantially as hereinbefore described with reference to any one of the Examples.

~~15. A compound of general formula II, IV, V, VI or VIa or process for the preparation thereof substantially as hereinbefore described or disclosed.~~

D A T E D this 9th day of June, 1977.

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